UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' REPLY BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT JON P. FRYZEK, MPH, PH.D.

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

I. INTRODUCTION

Dr. Fryzek's methodology and opinions are unreliable because he did not take into account a key data point: he has no idea what the highest level of NDMA/NDEA is in valsartan containing drugs ("VCDs"), or the ranges of NDMA/NDEA present in VCDs. This information was critical to the proper application of his purported methodology and its absence invalidates the process. Defendants only passingly address this fatal flaw towards the end of their brief in opposition, claiming without analysis that "Dr. Fryzek had no need to study the levels in the VCDs". (Def. Br. at 33 (ECF 1786).

II. ARGUMENT

A. Dr. Fryzek's Opinion that Valsartan and Valsartan-Containing Prescriptions are Not Associated with Cancer is Irrelevant and Will Mislead the Jury

Dr. Fryzek concluded that "[v]alsartan and valsartan-containing prescriptions are NOT associated with cancer." (Def. Br. at 2). However, the issue at hand in this case is not if valsartan is associated with cancer, but whether NDMA/NDEA can cause cancer. Plaintiffs have never alleged that properly manufactured, non-contaminated VCDs cause cancer – in fact, Plaintiffs agree that they do not. That is the point of the litigation. As a result, Dr. Fryzek should be precluded from opining that non-contaminated valsartan is not associated with cancer, as such testimony will only serve to waste trial time, and potentially confuse and mislead the jury. *Schneider ex rel. Est. of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003) (stating that "expert testimony must fit the issues in the case … [i]n other words, the expert's testimony must be relevant for the purposes of the case and must assist the trier of fact").

B. Dr. Fryzek's Methodology Requiring a Relative Risk in Excess of 2 for a Study to Be Relied on is Flawed and Requires Preclusion of Opinions Based on this Criteria

Dr. Fryzek's personal criteria requiring a relative risk of 2 or more before a study can suggest causation resulted in a flawed analysis of the dietary studies. (Fryzek Rpt. at 7, ECF 1713-3, Ex. A).

A. And then two, which means it's more likely than not. And so all of them have a confidence interval or a relative risk or hazard ratio or something that is two or less.

Q. Why is two more likely than not?

A. People - -

Q. You said two would be more likely than not. What did you mean by that?

A. Right. **Relative risk of two**.

Q. Why does it need to be two to be more likely than not?

A. **I believe that's what the courts have agreed as more of a litigation definition**.

Q. So outside of legal definitions, what would be more likely than not in epidemiology?

A. Oh, two. Relative risk or risk measure of two.

Q. And what does two represent?

A. Pardon me?

Q. What does the two represent? Is that like a doubling of the risk?

A. Yes.

Q. Why do you need a doubling of the risk to be more likely than not?

A. Because then you are less likely to have influence of confounders, bias, things like that.

Q. So you're less likely, but just because you're below two, doesn't mean that it's not more likely than not, correct?

A. I'm not sure.

(Fryzek Dep. 236:12-238:5, ECF 1786-3 (emphasis added)).

Upon then being confronted with studies indicating a relative risk greater than 2.0, Dr. Fryzek pivoted to an even more extreme position, claiming that the entire confidence interval needs to be greater than 2.0 and that the relative risk now needs to be 2.2:

A. So what we could take here, it shows in the graph that **the confidence interval is less than two.**

Q. I thought –

A. The relative risk –

Q. I thought it says 2.12.

A. That's not the confidence interval. That's the – that's the estimate.

Q. And so you're saying if any part of the confidence – if any part of the lower bound of the confidence interval is under two, it doesn't count?

A. **I'm not saying it's not more likely than not.** So you can see that in our graph.

Q. But the lowest end of the confidence interval is 1.04. The lowest end is still showing a four percent increased risk, correct?

A. Correct.

Q. How is that not more likely than not that it's increasing the risk of colorectal cancer.

A. **Because the definition of it has to be 2.2**.

Q. Whose definition?

A. Legal definition.

(Fryzek Dep. 241:6-242:9 (emphasis added)).

Dr. Fryzek's criteria is not consistent with the law. The District of New Jersey recently addressed this exact issue, "A relative risk of 2.0 means the risk has doubled, 'indicating that the risk is twice as high among the exposed group as compared to the non-exposed group.' In epidemiology, there is, however, no threshold, or a magical number, of a relative risk that must be found in order to place significant weight on the strength of association factor. Indeed, '[a] relative risk of 2.0 is not so much a password to a finding of causation as one piece of the evidence, among others for the court to consider in determining whether an expert has employed a sound methodology in reaching his or her conclusion." *In re Johnson & Johnson Talcum Powder,* 509 F. Supp. 3d 116 at 163-64 (2020) (citing *Magistrini*, 180 F. Supp. 2d at 606 (quoting *Landrigan v. Celotex Corp*., 127 N.J. 404, 419, 605 A.2d 1079 (1992)).

C. <u>Dr. Fryzek's Methodology is Unreliable as he Ignored the NDMA Levels in VCDs</u>

Dr. Fryzek's primary opinion is that "[t]he scientific evidence does not support an increased risk of cancer from the ***low levels*** of N-Nitrosodimethylamine (NDMA) or N-nitrosodiethylamine (NDEA) with the use of valsartan products." (Def. Br. at 2; Fryzek Rpt. at 1

(emphasis added)). In order for Dr. Fryzek to reliably opine that the scientific evidence does not support an increased risk of cancer from the levels of NDMA/NDEA in valsartan products, Dr. Fryzek must know the levels of NDMA/NDEA found to be present in VCDs.

However, when asked if he knew the ranges of NDMA in VCDs, Dr. Fryzek testified, "it wasn't important for my review." (Fryzek Dep. 106:6-9). Dr. Fryzek again confirmed later in his deposition that he did not know the minimum or maximum levels of NDMA in VCDs. (Fryzek Dep. 441:10-13). Defendants argue that "Dr. Fryzek had no need to study the levels in the VCDs" and cite *Adkisson v. Jacobs Eng'g Grp., Inc*., 2018 WL 3460244, at *14 (E.D. Tenn. July 18, 2018), *aff'd*, 2018 WL 4006782 (E.D. Tenn. Aug. 22, 2018) as support that an epidemiologist need not address dose and exposure in order to provide a reliable opinion related to general causation. (Def. Br. at 33). While it is true that an epidemiologist need not address dose and exposure in order to provide a reliable general causation opinion on whether NDMA/NDEA can cause cancer, Dr. Fryzek isn't seeking to opine that any amount of NDMA/NDEA can't cause cancer. He seeks to opine that the ***low levels*** of NDMA/NDEA in VCDs can't cause cancer.

Dr. Fryzek cannot reliably opine what the levels of NDMA/NDEA in VCDs are capable of causing, because Dr. Fryzek does not know what levels of NDMA/NDEA are in VCDs. (Fryzek Dep. 106:6-9; 441:10-13). Because it is impossible for Dr. Fryzek to reliably opine as to the risk posed by the levels of NDMA/NDEA in VCDs without knowing the levels of NDMA/NDEA in VCDs, his testimony should be precluded. *In re Zoloft (sertraline Hydrochloride) Prods. Liab. Litig*., 858 F.3d 745 (2017).

D. Dr. Fryzek's Knowledge Deficit Regarding Contamination Levels and Ranges in VCDs Prevented him from Adhering to his Inclusion and Exclusion Criteria

Defendants claim within their brief that Dr. Fryzek adhered to his inclusion and exclusion criteria, including studies "if they were observational studies of a group of people exposed to

valsartan, NDMA, or NDEA who developed cancer, ***compared to a group of unexposed or less exposed people***" and excluding studies "if they (1) were not cohort or case-control studies, i.e., case reports or narrative reviews, (2) studies animals or non-human laboratory testing, or (3) were not exposed to the necessary exposure, ***did not compare those exposed to those not***, or did not study cancer as a disease outcome." (Def. Br. at 17-18 (emphasis added)). In order for Dr. Fryzek to know if the two valsartan studies (*Gomm* and *Pottegard*) he relied on were actually able to compare those exposed to those not exposed or exposed to a lower amount of NDMA/NDEA, Dr. Fryzek would have to understand the contamination levels and ranges in VCDs. However, Dr. Fryzek repeatedly testified that he was not aware of the amount or ranges of NDMA in VCDs.

Q. Doctor, what's the highest levels of NDMA that you're aware of in a valsartan pill?

A. As I said, that wasn't important to my review.

Q. So you have no idea?

A. **I have *no idea*.**

Q. Do you know the ranges?

A. So my review found no relationship between valsartan and cancer.

Q. Do you know the ranges of NDMA in the valsartan pills?

A. As I said, **it wasn't important to my review**.

Q. And so that wasn't something that you considered when looking at the studies on valsartan contaminated with NDMA?

A. **That wasn't something that the authors of the studies considered**.

Q. But when you're looking at a study, do you not look for the strengths and weaknesses of that study?

A. I do.

Q. So did you not look into the levels of valsartan contaminations amongst the different manufacturers to see if there were any weaknesses in the studies that you cite?

A. I don't understand how that would be a weakness in epidemiology.

Q. Is the dose of NDMA in valsartan pills consistent amongst all valsartan pills?

A. Oh, that, **I don't know**.

Q. Excuse me?

A. That **I don't know**. I believe some of the studies that looked at valsartan tried to do a dose response relationship with various cancers and didn't find any dose-response relationship.

Q. What is a dose-response relationship?

A. Higher levels of valsartan cause more cancer. They just didn't see it in the studies.

Q. They didn't see higher levels of valsartan causing cancer or higher levels of NDMA?

A. Of – well, the NDMA in the valsartan.

Q. Do you know if they knew the levels of NDMA in the various valsartans?

A. That **I don't know**. I just know it was published in the paper.

(Fryzek Dep. 105:19-108:9 (emphasis added)). Dr. Fryzek's knowledge deficit was again confirmed at the end of his deposition.

Q. As far as the NDMA level in valsartan, **do you have *any idea* what the levels are**?

A. **No**.

(Fryzek Dep. 434:6-9 (emphasis added)).

1. <u>Valsartan Studies</u>

a. Gomm

Dr. Fryzek confirmed that the *Gomm* study, one of two valsartan studies that Dr. Fryzek relies on, was intended to investigate whether higher dosages of valsartan are more likely to cause cancer, in part, not whether higher levels of NDMA/NDEA cause cancer.

Q. [*Gomm*] notes the NDMA content of valsartan tablets seemed to correlate with the dose strength of the tablet. If that's inaccurate, is that going to impact the results of the study?

A. **I have no idea**.

Q. Why do you have no idea?

A. Because I don't know if it's true or not. And I don't know how it would impact the study.

Q. Well, is the study not trying to look at if higher levels of valsartan can cause cancer.

A. It was looking at a variety of questions. That was just one of them.

Q. Did they group people on exposure based on the milligram of the valsartan pill?

A. You'd have to show me that so I can recall that. **I don't recall** that off the top of my head.

Q. You don't recall how they did this study?

A. Not – not off – not off the top of my head, no.

Q. If they did classify people for exposure based in part off the milligram of the pill, and in reality some of the low milligram pills actually have more NDMA than the high milligram pills, would that impact the results of this study?

A. I'd have to – I'd have to see how they're classified. **I don't think it would impact the study though because there is no relationship between NDMA and cancer. I would say it would I still find no relationship.**[1]

Q. Don't you base your opinion that there's no association between NDMA and cancer in large part on this study?

A. Not in large part. The totality – the totality of the evidence.

Q. How many valsartan studies did you cite in your report?

A. Two.

Q. Two. And this is one of the two, right?

A. Right.

Q. And the validity of the results doesn't really matter how much NDMA is in the pills because you're already certain that NDMA is not carcinogenic in humans, right?

A. That's not what I–that's not what I said. I think they analyzed it a number of different ways.

Q. How?

A. **They looked at any valsartan use, valsartan use by different levels.**

(Fryzek Dep. 303:19-307:1 (emphasis added)). Comparing ever use of valsartan or various valsartan doses is not the same as comparing ever exposure to NDMA/NDEA or various doses of

[1] This testimony illustrates a major methodological flaw as Dr. Fryzek began his analysis with the assumption that NDMA cannot cause cancer in humans. Thus, he made the statement cited here that the relative levels of NDMA do not matter – in other words, he is saying that the NDMA doses stated in the studies relied on are irrelevant – contrary to every other expert in the litigation. He based this net opinion on his methodologically flawed criticism of the dietary studies, built in large part on his personal standard requiring a relative risk of 2. Of course, that is not required, and this is thus a house of cards that falls over easily on inspection. As to the dietary studies that did demonstrate a relative risk of 2 or more, he rejected those studies for various arbitrary reasons as well, such as the lower bound of the confidence interval being below two.

NDMA/NDEA.[2] Therefore, *Gomm* should not have met Dr. Fryzek's inclusion criteria and should have met his exclusion criteria.

b. Pottegard

Pottegard, the other valsartan study relied on by Dr. Fryzek, suffers from the same fundamental design flaw as *Gomm*—both assume that milligrams of valsartan were an appropriate way to scale for NDMA content in the pills, in the absence of reliable data as to the existence or levels of NDMA in the pills.[3] To be clear, one must know the parts per million ("ppm") of the NDMA in the API batch to calculate the NDMA level in the pill. Only with that information does the milligrams of the pill become informative. For example, batches of ZHP API varied in NDMA and NDEA levels by extraordinary amounts, even when utilizing the same manufacturing process.[4] A 320 mg pill containing ZHP manufactured valsartan API from a batch with 5 ppm of NDMA would have a quite different NDMA level from a pill utilizing an API batch with 160 ppm of NDMA.[5] The contamination level of the API utilized in the pill is the most appropriate method of determining the contamination level. Dr. Bottorff, Defendants' pharmacology expert agrees:

> Q. So would you agree with me that it would be more appropriate to use the ppm of the API than the final product?
>
> A. I would agree with that.

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[2] Of note, when *Gomm* removed the milligram of the pill from the equation and only considered if the pill was *potentially* contaminated with NDMA (misclassification by including non-contaminated VCDs, including those exposed to less than 96 nanograms per day, and including those who only filled one contaminated prescription still weakened any signal) and looked at a single organ, *Gomm* was able to detect a statistically significant increased risk of liver cancer (hazard ratio: 1.16 [1.03; 1.31]). (*Gomm* at 360, ECF 1717-7). However, the signal did not meet Dr. Fryzek's arbitrary standard of a 2.2 relative risk.

[3] Etminan Rpt. at 26, ECF 1717-3; Panigrahy Rpt. at 95-96, ECF 1716-3; Hecht Rpt. at 16-17, ECF 1714-3; Lagana Rpt. at 26, ECF 1718-4.

[4] ZHP had a manufacturing process for valsartan API that resulted in batches ranging from 0.3 ppm to 240.1 ppm, even though all batches are identified by the same product code. (ZHP02563327 at ZHP02563368, Ex. S).

[5] Furthermore, if the API has 0 ppm of NDMA, then the final pill would not contain NDMA, regardless of the milligram of the pill.

(Bottorff Dep. 34:9-13, ECF 1712-3).

It is noted in the "Ascertainment of NDMA exposure" section of the *Pottegard* study that "[t]he use of milligrams of valsartan as a scale for the dose-response analysis was based on the observation that the NDMA content for each tablet seems to correlate with the strength of the tablet."[6] (*Pottegard* at 2, ECF 1717-8). We know this to be inaccurate statement since the NDMA contamination levels widely varied by batch, even batches produced by the same manufacturer.

Had Dr. Fryzek looked at the FDA's published information on VCD contamination levels and ranges, or internal company documents that provide significantly more information on contamination ranges, then he would have known that the two valsartan studies he relies on to opine that "[t]he scientific evidence does not support an increased risk of cancer from the low levels of N-Nitrosodimethylamine (NDMA) or N-nitrosodiethylamine (NDEA) with the use of valsartan products" did not meet his inclusion criteria and did meet his exclusion criteria. This gap prevented him from reliably applying his own methodology, rendering his opinion unreliable.

2. <u>Ranitidine Studies</u>

In addition to the two valsartan studies, Dr. Fryzek also relied on two ranitidine studies (*McGwin* and *Yoon*) in coming to his opinion that "[t]he scientific evidence does not support an increased risk of cancer from the low levels of N-Nitrosodimethylamine (NDMA) or N-nitrosodiethylamine (NDEA) with the use of valsartan products." Dr. Fryzek's reliance on these two ranitidine studies is flawed for the same reasons as his reliance on the two valsartan studies; Dr. Fryzek does not know the levels or ranges of NDMA/NDEA in valsartan or ranitidine.

Q. What levels of NDMA are in ranitidine?

A. Oh, **I have no idea**.

[6] *Pottegard's* only reference for this assumption is a foreign website: https://www.pharmazeutische-zeitung.de/index.php?id=77660. (*See Pottegard* at 7, reference 14).

Q. And how is that applicable to if the NDMA in valsartan causes cancer?

A. They were another way to look at the data, to look at NDMA. So we just included them.

Q. But **you have no idea how much NDMA is in ranitidine?**

A. **No. It wasn't important to the studies so.**

Q. Even if it's not important to the studies, is it not important to your analysis on if that's applicable to the amount that is in valsartan?

A. I'm not clear how we would analyze it unless the authors reported it.

Q. Well, if you're not clear on how to analyze it, then why did you include it in your expert report?

A. I didn't say I wasn't clear how to analyze it. I said I'm not sure how I would use that information if it's not reported.

Q. Would that not be valuable information if it was reported?

A. I'm sorry. I didn't understand.

Q. If the levels of NDMA in ranitidine were reported, would that not be important information for you to consider?

A. I have no idea. I just reported on what the authors of the studies reported.

Q. In your opinion, **is there more or less NDMA in ranitidine than valsartan?**

A. Well, **I have no idea**, but neither type of study showed any risk of cancer. So that's comforting.[7]

(Fryzek Dep. 122:11-124:14 (emphasis added)).

Dr. Fryzek has no idea how much NDMA or the ranges of NDMA that were present in the ranitidine studies he relied on as well. Dr. Fryzek also has no idea how the NDMA levels and ranges in ranitidine compare to the NDMA levels and ranges in valsartan. Allowing Dr. Fryzek

[7] Incredibly, in applying his methodology, Dr. Fryzek did not factor in that *Gomm* found a statistically significant increased risk of liver cancer from intake of contaminated valsartan, based on cautionary language in the study regarding the need for longer studies, and the fact that two other studies (*Pottegard* with a far smaller sample size and *Yoon*, a ranitidine study) did not make this finding. (Fryzek Rpt. at 18). The failure to give this finding any weight is a fatal methodological flaw. An expert cannot establish a preference for study findings based on the conclusions reached as this simply amplifies bias. This is an insurmountable problem for the application of this methodology.

to opine that ranitidine isn't associated with cancer and that this is relevant here would have the same result as allowing Dr. Fryzek to opine that valsartan isn't associated with cancer—misleading and distracting the jury from the real issue at hand—does NDMA/NDEA cause cancer.

E. Dr. Fryzek Should be Precluded from Opining the Levels of NDMA Exposure in Hidajat are Not Similar to the NDMA Levels from Contaminated Valsartan

Dr. Fryzek opines that "[i]t is absurd to suggest that workers in [*Hidajat*] had similar levels of exposure to NDMA as valsartan users" (Fryzek Dep. 440:8-12; Fryzek Rpt. at 52). Yet again, Dr. Fryzek has no idea how much NDMA is in VCDs or the exposure levels in *Hidajat*, and did not even account for the levels in general, so this is a classic net opinion:

Q. Doctor, **what were the NDMA levels in valsartan?**

A. So that, **I don't know**. The workers in Hidajat were breathing in NDMA. And valsartan you take orally. So it's a different exposure route.

Q. Why does that matter?

A. Because carcinogens act differently depending on how they are taken, how they're, you know, taken into the body.

Q. And how is NDMA going to act differently if it's inhaled versus taken orally?

A. That, we don't know. But it's not the same exposure.

Q. Would different organs be susceptible because it's through air as opposed to oral?

A. You know, I have no idea. But it's not the same exposure route.

Q. And again, **you have no idea of the minimum or the maximum levels of NDMA in any valsartan pills, correct?**

A. **I don't. Or in the Hidajat study, we don't know what the levels are there either**.[8]

(Fryzek Dep. 440:13-441:15 (emphasis added)).

Dr. Fryzek can not reliably opine that the levels of NDMA exposure in *Hidajat* are not similar to the levels of NDMA that some valsartan users were exposed to if he does not know the

[8] Plaintiffs' expert, Dr. Madigan calculated the NDMA exposure levels in *Hidajat*. (Madigan Rpt. at 8, ECF 1715-4).

levels of NDMA exposure in *Hidajat* or the levels of NDMA exposure experienced by contaminated valsartan users.

III. CONCLUSION

For the foregoing reasons, Dr. Fryzek should be precluded from offering any opinions related to general causation.

Dated: Jan. 6, 2022

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on January 6, 2022, a true and correct copy of the foregoing was filed and served upon all counsel via operation of the CM/ECF system for the United States District Court for the District of New Jersey.

/s/ C. Brett Vaughn
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